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Emergence of spontaneous seizures during the year following lithium/pilocarpine-induced epilepsy and neuronal loss within the right temporal cortices

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Abstract

Thirty days after the induction of seizures in 16 rats with lithium (3 mEq/kg) and pilocarpine (30 mg/kg), the numbers of episodes of motor seizures (rapid forelimb clonus) during daily 10-minute observational periods were recorded for 11 months. The proportions of neuronal loss were ranked using two methods by light microscopy for all structures between the posterior and anterior commissures. Amounts of damage within the dentate gyrus, hilus (CA4), and CA3 field were most strongly correlated with numbers of seizures per month about 6 months before the brains were removed. The strongest correlations occurred between the amounts of damage within the right temporal cortices, even after the variance associated with damage within the dentate gyrus had been removed, and the numbers of seizures during the last 2 months. These results may explain the greater proportion of spontaneous seizures that begin with left side forelimb clonus and suggest a particular sensitivity of the right side of the brain to either their initiation or their consequences.
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1. Introduction

According to Fujikawa [1] mild histological damage is evident within the hippocampal formation and severe damage is evident within the entorhinal cortices, hilar region of the dentate gyrus, amygdala, and CA1 region of the hippocampus within 24 hours of 3 hours of pilocarpine-induced status epilepticus. Similar patterns of damage for lithium- and pilocarpine-induced seizures were reported by Motte et al. [2]. Neuronal losses within large portions of the amygdala, thalamus, basal ganglia, and cerebral cortices continue during the weeks following the induction of seizures with lithium and pilocarpine [3].

After a silent period of between 4 and 44 days, rats in which status epilepticus (SE) had been induced by a single systemic injection of lithium (3 mEq/kg), followed by pilocarpine (30 mg/kg) 4–24 hours later, or a single injection of pilocarpine (380 mg/kg) exhibit spontaneous seizures [4]. The overt manifestations of these brief (about 30 seconds) events include forelimb clonus, rearing, and falling, similar to Racine's [5] stage V seizures that emerge during kindling, and last the rest of the animal's life [6]. During both the silent and chronic periods, mossy fibers sprout within the inner molecular layer throughout the septotemporal axis of the hippocampus [6].

We [7] have developed a simple protocol for the daily observation of spontaneous seizures. Following the introduction of a Purina food cube into the home cage, rats that have entered the chronic stage of spontaneous seizures display these overt behaviors within 10 minutes. The unmistakable overt displays do not occur every day for each rat, but are sufficiently frequent to allow experimental manipulation or to yield strong correlations with external variables [8]. The present study was designed to discern if the incidence of spontaneous seizures changed during the year that followed the induction of

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status epilepticus with lithium and pilocarpine, followed by acepromazine (to facilitate survival), and if the numbers of seizures were associated with the amount of neuronal loss within specific regions of the brain. Because the first and most consistent areas that show necrosis in pilocarpine, lithium/pilocarpine, and perforant pathway stimulation treatments have been the CA3 field, the hilus of the dentate gyrus (CA4), and the dentate gyrus [1–3], the source of mossy fibers, we focused on these structures.

2. Method

2.1. Subjects and drug administration

After approval by the university's research ethics committee, and in accordance with the Council for Canadian Animal Care guidelines, 24 male Wistar rats were obtained from Charles River when they were about 60 days of age. After 2 weeks of habituation to the colony conditions, they were injected subcutaneously with 3 mEq/kg lithium chloride (3 mEq/cc) and then, 4 hours later, with 30 mg/kg pilocarpine. All rats displayed rearing, forelimb clonus, and falling within about 45 minutes. These behaviors are associated with clear electroencephalographic signatures of epileptic activity [9]. About 60 minutes after injection of the lithium each rat was injected subcutaneously above the scapula with 25 mg/kg acepromazine (Atravet) to help reduce mortality.

The rats were returned to single cages and maintained in isolation (to prevent fighting and to facilitate observation) for the remainder of the study. Six hours later each rat received 1 mg/kg atropine sulfate subcutaneously. The colony was maintained under a 12:12 light/dark cycle (lights on 08:00 hours) and the temperature was regulated within 1 °C around 20 °C. Purina rat chow was available ad libitum.

2.2. Observations of spontaneous seizures

One month after the induction of the seizures, two Purina cubes were placed each day in each cage about 10–30 minutes before the onset of darkness (20:00 hours). Even though the rats were maintained on food ad libitum, this procedure evoked socially facilitated eating, and the occurrence of occasional spontaneous seizures [7,8]. The numbers of overt seizures (similar to Racine stage V) exhibited during the first 10 minutes after addition of the food cubes were recorded.

2.3. Histology

Eleven months later (1 year after induction of the seizures), the 16 rats that were still alive were decapitated. The other 8 rats had died suddenly during the year or were terminated because their body weights were below 70% of the free feed values, the endpoint criterion for the animals employed in this study. The brains were quickly removed and fixed in ethanol–formalin–acetic acid. After processing, 10-μm coronal sections were obtained by microtome between the posterior and anterior commissures. Every 10th section was stained with toluidine blue O. This method of fixation, processing, and staining results in very clear histomorphology and minimal artifacts [10].

Each section was examined at 400× and 100× magnification by light microscopy according to Persinger et al. [10]. For this procedure, the presence or absence of neuronal dropout for each slide that contained all of the structures defined by Paxinos and Watson [11] within the space between the two commissures was measured. The proportion of damage for each structure was defined by dividing the number of sections for a structure that contained this measure of nominal (0,1) damage by the total number of sections occupied by this structure, and multiplying by 100.

Consequently, if there were 8 sections containing the structure and 4 contained clear evidence of necrosis, the proportion of damage was 50. Each structure's score was derived from observation of between 2 and 10 sections. The validity of this method of inference regarding neuronal dropout or brain damage has been indicated by the strong ($r > 0.80$) correlations between quantitative measures of behaviors associated with those structures [12,13]. The histopathologist for these measures was unaware of the behavioral history of the rats from which the brains were extracted.

The damage scores were calculated separately for the same structure on the left and right sides. Because of the large numbers of structures designated by Paxinos and Watson [11] within the volume we measured, and to facilitate an appreciation for the overall damage, the mean scores for "classic" regions were calculated by computer software. For example, the score for the "basolateral amygdala" was the mean of the scores for the subcomponents (see [11] for details) BMP, BLA, BLV, BM, BMA, LADL, LAVM, LAVL, and LA, and the score for the temporal cortex was the mean for TE1, TE2, and TE3.

In response to suggestions by referees, a second system of measurement was devised that approximated the amount of damage in the CA1, CA2, CA3, CA4, and dentate regions from 0 to 10, where 5 was 50% neuronal loss, 8 was 80% neuronal loss, etc. The reference for 0 was normal brains that were employed as visual references just before each structure was rated. Interrater reliability for 20 sections randomly selected from different brains with a range in levels of damage was about 0.85. There were six slides equally spaced between the rostral and caudal extents of the dentate gyrus for each

rat. The correlations between the scores for this system and the actual numbers of neurons per square millimeter in various amygdaloid and thalamic nuclei have been between −0.85 and −0.95.

2.4. Data analysis

Because our measures of brain damage were ranks, nonparametric correlations (Spearman rho) were completed between the total numbers of seizures observed during the 10-minute daily periods per month and the rating of neuronal damage within each of the structures on the left and right sides of the brain. Pearson correlation coefficients were calculated to examine the potential role of outliers. Partial correlation analyses were completed separately between the numbers of seizures per month and the mean rank of the damage within the three areas of the temporal cortices and the dentate gyrus for the left and right sides of the brains. All analyses involved SPSS software on a VAX 4000 computer.

3. Results

The numbers of seizures per month for each rat that survived to the end of the experiment are listed in Table 1. The means and SD for the proportion of damage within the major or "classic" larger regions for the left and right sides of the brains are listed in Table 2. The histomorphological characteristics of the damage reflected the usual neuronal dropout, gliosis, and accumulation of densely stained calcium-containing aggregates of Nissl material, pictures of which from previous experiments have been published elsewhere [3]. Single paired t tests indicated no significant ($P > 0.05$) differences in damage between the left and right sides for any of the regions.

Table 3 lists all of the statistically significant Spearman rho correlation coefficients between the numbers of seizures during the month before removal of the brains and the amount of neuronal damage in specific structures. The individual differences for the numbers of seizures per month over the period were representative of our observations. Some rats displayed the occasional seizure almost monthly, whereas other rats displayed quiet periods for several months followed by increased numbers of spontaneous seizures. The Spearman rho and Pearson r values for the total numbers of seizures for the whole group as a function of months since the induction of status epilepticus were 0.69 and 0.71, respectively.

Table 4 lists the correlation coefficients between the numbers of seizures per month for each of the 11 months preceding the removal of brains and the ranking of brain damage within the different fields of the hippocampus, dentate gyrus, and different regions of the temporal cortices for the left and right sides of the brain. There were twice the number of statistically significant correlations between ranking of brain damage and numbers of seizures for the right side of the brain compared with the left side of the brain.

Two "clusters" of the strongest and most persistent correlations can be visualized from Table 4. The first involves the amount of damage within the right temporal cortices and the numbers of seizures during the months before the brains were removed. The second involves the amount of damage within the dentate gyrus and CA4 and CA3 fields of the hippocampus and the numbers of seizures 5–6 months before the brains were removed.

Partial correlation analyses between the statistically significant zero-order correlations between the amounts

Table 1
Numbers of spontaneous seizures per month for each rat whose brain was examined

Rat	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun
8445	0	2	0	1	0	0	0	1	0	0	0
8449	2	0	0	1	2	2	0	1	0	1	1
8451	6	1	2	0	2	2	2	1	0	4	5
8452	1	0	2	1	1	0	0	0	0	0	0
8455	0	1	0	1	1	0	0	0	1	0	0
8456	1	0	0	0	4	3	2	1	2	2	3
8459	5	1	0	0	4	5	0	0	2	0	0
8461	0	2	4	1	0	0	0	0	0	3	5
8469	1	1	0	0	2	0	0	4	3	3	4
8470	0	4	0	1	1	5	4	5	3	7	9
8471	2	0	0	1	1	1	0	3	1	2	4
8473	4	1	0	1	4	1	0	1	4	3	5
8474	0	0	1	0	0	0	2	1	2	0	1
8476	0	0	0	7	4	5	4	4	4	5	8
8477	1	0	0	1	1	0	2	0	1	5	6
8479	0	0	0	0	2	2	1	0	2	1	4
8480	1	0	0	0	0	0	0	0	1	0	0
Total	24	13	9	16	29	26	17	22	26	36	55

Table 2
Proportion of damage within the major nuclear aggregates and structures in the left and right sides of the thalamus and telencephalon in rats ($n = 17$) the daily seizures of which were observed for 9 months

Structure	Left		Right	
	Mean	SD	Mean	SD
Entorhinal region	11	11	14	14
Subiculum	2	3	3	4
CA fields of hippocampus	26	10	31	18
Dentate gyrus	11	17	11	15
Occipital cortex	2	5	3	4
Retrosplenial cortex	0	0	0	0
Cingulate cortex	0	0	0	0
Temporal cortex	10	13	12	16
Parietal cortex	26	33	31	32
Frontal cortex	7	11	9	14
Insula cortex	6	11	7	12
Orbital cortex	0	0	0	0
Piriform cortex	28	22	30	23
Endopiriform nucleus	2	5	3	3
Substantia nigra	4	8	3	5
Caudate putamen	5	8	9	15
Amygdalostriatal transition	0	0	1	2
Pallidum	0	0	1	4
Ventral striatum	0	0	0	0
Olfactory tubercle	0	0	0	0
Corticoamygdala	12	13	13	11
Amygdalohippocampal transition	2	6	2	6
Basolateral amygdala	8	11	6	11
Medial amygdala	2	4	11	18
Central nuclei of amygdala	0	0	0	0
Intercalated nucleus	0	0	1	2
Anterior amygdala	0	0	9	17
Thalamus				
Medial geniculate	11	10	13	9
Posterior thalamic group	16	9	13	8
Lateral posterior group	71	24	71	25
Lateral dorsal group	50	24	60	24
Intermedullary area	27	36	16	23
Lateral geniculate	4	3	2	2
Habenulae	0	0	2	2
Ventral group	11	10	13	14
Intralaminar group	15	13	16	10
Midline nuclei	37	6	35	9
Mediodorsal group	32	6	31	9
Anterior group	3	6	7	12
Extended amygdala	0	0	0	0
Septum	4	9	3	9

of damage within the temporal cortices in the left hemisphere and numbers of seizures per month were eliminated if the shared variance between the temporal cortices and dentate gyrus was first removed. On the other hand, the partial correlations (all $df = 14$) between the amount of damage within the left dentate gyrus and numbers of seizures during November (0.59), December (0.51), April (0.58), and June (0.46) remained or became significant statistically when the shared variance between damage within the dentate gyrus and that within the temporal cortices was first removed.

Table 3
Structures displaying statistically significant ($P < 0.05$) Spearman correlations between numbers of seizures in the month before the brains were removed and the rating of damage for the left and right sides of the brain

Left side		Right side	
Temporal cortex 2	0.43	Presubiculum	0.42
Parietal cortex	0.45	CA2 hippocampus	0.46
Caudate putamen	0.52	Occipital cortex 2L	0.42
Lateral amygdala (VL)	−0.45	Occipital cortex 2ML	0.42
Lateral amygdala (L)	−0.46	Temporal cortex 2	0.50
Supragenicuiate	0.45	Temporal cortex 1	0.65
Medial geniculate	0.46	Temporal cortex 3	0.43
Lateral posterior (MR)	0.45	Medial amygdala (PV)	−0.45
Reuniens (ventral)	0.41	Medial amygdala (AV)	−0.57
Medial dorsal (cen)	−0.42	Medial geniculate (ventral)	0.46
Septohypothalamic nuclei	−0.45	Medial dorsal nuclei	0.60
		Septohypothalamic nuclei	−0.45

On the other hand, for the right side of the brain, the partial correlations between the amount of damage within the temporal cortices and numbers of seizures during February (0.45), May (0.44), and June (0.55) remained significant statistically, even when the shared variance between damage in the temporal cortices and that in the dentate gyrus was first removed. When the shared variance between these two structures was removed first, the partial correlations between damage within the right dentate gyrus and numbers of seizures during November (0.46), December (0.52), January (0.42), March (0.58), and April (0.47) remained statistically significant.

The Spearman rho correlations for the comparisons between the nominal ranking system and the one instituted for this study, in which the proportion of neuronal dropout was ranked from 0 to 10 (100%) for each structure for each section immediately after viewing control brains, ranged between 0.65 and 0.80. Only the scores for the rostral two (of six) sections of the left dentate gyrus were significantly correlated with the averaged nominal scores (0.76, 0.75) of the main study. For the right dentate gyrus only the score for the middle portion was correlated significantly (0.63) with the nominal scores. For the CA3 field, only the scores for the caudal half (three slides) of this area in this side only was correlated significantly (0.64, 0.72, 0.80) with the averaged nominal scales.

4. Discussion

The results of these quantitative analyses for ranks of brain damage and the monthly scores for the daily sampling of overt seizures indicated that the strongest association occurred in the proportion of neuronal

Table 4
Spearman correlations between the numbers of seizures per month and the rating of damage within the components of the hippocampal formation and temporal cortices on the left and right sides

Structure	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun
Left side											
DG	0.10	0.03	0.00	0.34	0.43*	0.35	−0.08	0.22	0.45*	0.28	0.31
CA4	0.47*	0.13	0.02	0.29	0.50*	0.46*	−0.01	0.38	0.31	0.28	0.24
CA3	−0.15	−0.12	−0.02	0.49*	0.18	0.41*	0.10	0.21	0.08	0.28	0.36
CA2	−0.37	0.17	0.32	0.35	−0.04	0.28	−0.17	−0.08	0.00	0.12	0.09
CA1	−0.48*	0.13	0.46*	−0.08	−0.54*	−0.27	−0.04	−0.08	−0.36	−0.18	−0.11
TCtx 1	−0.28	−0.23	−0.27	0.43	−0.06	0.19	0.31	0.09	−0.04	0.26	0.30
TCtx 2	−0.46*	−0.30	−0.15	0.12	0.03	0.33	0.66*	0.20	0.35	0.28	0.43*
TCtx 3	−0.30	−0.14	−0.25	0.05	0.06	−0.21	0.07	−0.49*	−0.02	−0.04	0.00
Right side											
DG	0.20	−0.12	−0.13	0.25	0.58*	0.51*	0.15	0.53*	0.47*	0.38	0.36
CA4	0.45*	0.11	0.04	0.03	0.64*	0.47*	0.14	0.54*	0.32	0.40	0.29
CA3	0.22	−0.13	−0.26	0.04	0.70*	0.45*	−0.04	0.31	0.42*	0.12	0.04
CA2	−0.28	0.27	−0.05	0.40	−0.10	−0.13	0.09	0.29	0.01	0.52*	0.46*
CA1	−0.26	0.09	0.50*	−0.11	−0.36	−0.16	0.00	0.04	−0.36	−0.08	−0.07
TCtx 1	−0.01	−0.15	−0.28	0.11	0.19	0.32	0.49*	0.32	0.17	0.65*	0.65*
TCtx 2	−0.27	−0.01	−0.35	0.07	0.49*	0.62*	0.54*	0.31	0.66*	0.43*	0.50*
TCtx 3	−0.45*	0.08	−0.39	0.08	0.15	0.13	0.39	0.18	0.48*	0.42*	0.43*

* $P < 0.05$.

dropout within the dentate gyrus and temporal cortices within the right side of the brain. There were also twice the number of statistically significant correlations between the numbers of seizures per month and the ranked damage within components of the hippocampal formation and different regions of the temporal cortices for the right side compared with the left side, despite the similarity of the magnitudes of the damage as reflected by group averages.

The reduction of the magnitudes of the correlations between damage within the temporal cortices in the left side of the brain, once its shared variance with the damage in the left dentate gyrus had been accommodated, indicates that this association may have been spurious and due to the source correlation between the numbers of seizures and damage within the dentate gyrus. On the other hand, the correlations between the amount of damage within the right temporal cortices and numbers of seizures remained significant statistically, even though the shared variance with damage within the dentate gyrus on that side had been accommodated.

The presence of significant correlations and partial correlations between the numbers of seizures and proportion of damage in the right temporal lobe would be congruent with the behavioral observations that more than two-thirds of all "spontaneous" seizures began with clonus of the left forepaw. Because there was no significant difference in the proportion of neuronal dropout between the right and left temporal cortices, one would expect that some process other than gross loss of neurons could be mediating these correlations.

There are obvious possibilities. For example, either the types of neurons damaged by the consequences of the seizures or the specific subtypes of receptors altered during the subsequent evolution of spontaneous seizures may have differed between hemispheres. In this case, the correlation between damage within the right temporal cortices (but not the left) and overt seizures during the period before the brains were removed might reflect a dynamic process in response to the repetitive seizures during the previous 6 months.

If we assumed that damage within specific structures progresses and asymptotes, as indicated by our previous research [3,13], then a possible source for the association between right temporal lobe damage and numbers of seizures might be identified. In the present study, the proportion of damage within the dentate gyrus and adjacent hippocampal regions was positively correlated with the numbers of seizures during the 5–6 months before the brains were removed. If we assumed that this configuration of damage allowed more seizures to occur and to be propagated to the right temporal cortices during the subsequent 6 months, then the specific correlation between neuronal loss within the right temporal cortices and seizures during this period might be explained.

One frequent quote in the scientific literature is that the silent seizure-free period subsequent to the induction of status epilepticus lasts about 4–44 days before all animals exhibit spontaneous recurrent seizures. The most obvious candidate for the emergence of spontaneous seizures has been the intense sprouting of mossy fibers within the inner molecular layer along the entire septotemporal axis of the hippocampus [2]. This growth is likely to occur in response to cell death within dentate hilus (CA4) and gyrus that begins within a few hours of status epilepticus. The subsequent failure of $GABA_B$ receptor-mediated modulation of mossy fiber transmission

at mossy fibers has been hypothesized as a major contribution to the development of spontaneous seizures after status epilepticus [14].

Our more gross quantitative results suggest that either the proliferation of mossy fibers continued long after the "silent" period or a different process emerged during the months of spontaneous seizures that followed the silent period. The significant correlations between the amount of damage within the dentate gyrus, CA4 (the hilus of the dentate gyrus), and CA3 within both hemispheres at the times the brains were removed and the numbers of seizures 6–7 months previously would be consistent with a resurgence of growth of mossy fibers during this period that promoted the occurrence of more seizures.

Because few researchers have followed the progress of the spontaneous seizures or their neuropathological or electrophysiological correlates for such long periods, the existence of recursive sprouting may not have been realized. Both the data presented in Table 1 and our observations have shown that most rats during the chronic period, during the months that follow the induction of status epilepticus with lithium and pilocarpine, exhibit at least one episode that appears similar to the original response produced by these drugs. The rats usually seize many times within the same day, do not eat for about 3 days, and lose weight. If they do not die or must be killed to accommodate guidelines for animal care, these rats exhibit another "silent period," followed by the return of spontaneous seizures. We speculate that this "temporal lamination" of several cycles of newer mossy fibers superimposed on and intercalated with previous fibers induced by reactive synaptogenesis could foster emergent properties.

We suggest that the strong correlations observed between the numbers of seizures during the 2 months before the brains were removed and damage within the right temporal cortices may have involved a process related to kindling. We cannot exclude the possibility that correlations between the amounts of damage within the medial geniculate and the temporal cortices may have been iatrogenic. Previous research suggests that excessive stimulation by exposure to proprioceptive/touch or auditory stimuli exacerbates the neuronal dropout within the regions of the brain that receive or modulate these stimuli in the brains of these rats [13]. In the present study the daily sounds of food dropping into the cage, which becomes a conditioned stimulus for spontaneous eating [7], may have increased necrosis in populations of neurons already compromised. However, we hypothesize that the more frequent initiation of the seizures within the right side of the brain, as indicated by the preponderance of overt displays beginning with left forelimb clonus before bilateral generalization, may have contributed to the neuronal dropout within the right temporal cortices.

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